SYSTEMATIC / NARRATIVE REVIEW ARTICLE

The role of apolipoproteins as genetic biomarkers in schizophrenia: A systematic review

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ABSTRACT

Introduction: Schizophrenia is a complex mental disorder involving genetic, environmental, and neurodevelopmental factors. Despite significant progress in identifying several genetic contributors to schizophrenia, the role of apolipoprotein in lipid metabolism, neurodevelopment, and neuroprotection remains underexplored. This systematic review aims to synthesise existing genetic studies on apolipoproteins associated with schizophrenia to clarify their potential role in the disorder's pathogenesis.

Materials and Methods: A comprehensive literature review was conducted using the PubMed and Scopus databases, involving studies published from 2004 to 2023, and limited to English. Keywords included "schizophrenia," "apolipoprotein," "genetic," and "genetics." Non-research publications such as books, reviews, editorials, letters to editors, short communications, book series, chapters, and conference proceedings were excluded from this review. Only peer-reviewed journal articles were selected to ensure the reliability and credibility of the systematic review.

Results: A total of 41 articles were included in the review, with four key themes identified. The themes addressed specific aspects of apolipoproteins in schizophrenia, including their role in schizophrenia susceptibility, lipid metabolism, and cognitive functions within the disorder. This review presents a novel synthesis of these studies, focusing on the underexplored roles of apolipoprotein genes, including *APOE*, *APOL*, *APOD*, *APOA*, *APOC*, *APOER2*, and *APOBEC*, in schizophrenia.

Conclusion: This systematic review provides a comprehensive understanding of the genetics of apolipoprotein in schizophrenia, particularly in relation to lipid metabolism. The findings suggest future research directions to enhance the understanding of schizophrenia pathogenesis and highlight the importance of targeted research to identify specific genetic biomarkers for therapeutic interventions.

KEYWORDS:
Genetics, apolipoprotein, lipid metabolism, schizophrenia, systematic review

INTRODUCTION

Schizophrenia is a complex, multifactorial neuropsychiatric disorder influenced by genetics, environment, and neurodevelopment.[1] According to the World Health Organisation, in 2022, this condition affects approximately one in 300 people worldwide, or around 24 million individuals.[2] Those with schizophrenia experience symptoms such as hallucinations, delusions, disorganized thinking, and cognitive impairment.[3] While the heritability of schizophrenia is estimated to be as high as 80%, the specific genetic pathways contributing to its development remain only partially elucidated.

A growing body of research links lipid dysregulation to cognitive dysfunction and structural brain abnormalities in schizophrenia. Apolipoproteins are key regulators of lipid transport, cholesterol homeostasis, neuroinflammation,[4] neuronal repair, and synaptic plasticity.[5] Given these roles, apolipoprotein genes are biologically plausible candidates in schizophrenia, as variations in these genes may affect neurodevelopmental pathways, inflammatory responses, and metabolic profiles, all of which are implicated in the disorder.

Apolipoproteins comprise several families, including *APOA, APOBEC, APOC, APOD, APOE, APOER2*, and *APOL*. Although apolipoprotein E *(APOE)*, particularly ε2, ε3, and ε4 alleles, has been investigated extensively in neurodegenerative disorders,[6] the other apolipoprotein genes have recently attracted attention for their potential involvement in schizophrenia. However, their collective roles in disease susceptibility, cognitive outcomes, treatment response, and metabolic disturbances remain inadequately explored.

A previous systematic review focused mainly on the genetics of *APOE* in schizophrenia.[7] To date, no systematic review has

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synthesised the broader family of apolipoprotein genes or evaluated their potential as genetic markers in schizophrenia. Since apolipoproteins affect pathways linked to both psychiatric pathology and metabolic side effects of antipsychotics, a comprehensive synthesis is necessary to clarify their biological and clinical relevance. This systematic review aims to fill that gap by assessing existing research on apolipoprotein families in schizophrenia, offering a clearer understanding of their potential roles as genetic indicators. Specifically, this review aims to answer the following questions:

1. Which apolipoprotein genetic variants may serve as potential biomarkers of schizophrenia susceptibility and diagnosis?
2. Which variants may influence clinical course or predict treatment response?
3. Which variants may predict metabolic abnormalities commonly observed in schizophrenia, particularly those associated with antipsychotic therapy?
4. Which variants may predict cognitive performance or impairment among individuals with schizophrenia?

By synthesizing findings across multiple apolipoprotein gene families, this review seeks to provide a clearer understanding of their potential roles as genetic biomarkers in schizophrenia.

MATERIALS AND METHODS

Review Protocol

This systematic review involves formulating the research questions using the PICo method: 'P' for Problem or Population, 'I' for Interest, and 'Co' for Context, which is a tool employed by authors to develop research questions for the review.[8,9] A systematic document search was conducted in three phases: identification, screening, and eligibility.[10] The review also includes data extraction and qualitative data analysis.[9] Throughout the process, the authors consider alternatives to ensure alignment with the aim of the review.

Formulation of Research Question

Based on the PICo concept, the authors incorporated three major elements into the review population (P) of schizophrenia patients, interest (I) in genetic studies, and the context (Co) of apolipoprotein. This framework directs the formulation of the main research question: What are the genetic studies related to apolipoprotein in schizophrenia?

Identification

Two investigators (WNFWMZ and NEHAR) conducted a systematic search strategy using PubMed and SCOPUS databases. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. The search strategy was developed using relevant keyword recognition, including "genetic," "schizophrenia," and "apolipoprotein," as detailed in the search string in Table I. All possible synonyms were included using appropriate Boolean operators and filters. The search was conducted on January 9th, 2025.

Screening

Original articles from peer-reviewed journals published in English between 2004 and 2023 were included. Non-research documents such as reviews, editorials, letters to the editor, short communications, books, book series, chapters, and conference proceedings were excluded to avoid potential bias and ensure that only studies with rigorous methodologies were considered. Two reviewers (NAT and MAK) independently screened all records retrieved during the search using predefined inclusion and exclusion criteria. Duplicate records and studies that did not satisfy the requirements were all discarded. Inter-rater reliability for the full-text screening stage was assessed using Cohen's kappa statistic. Out of 66 screened articles, the reviewers agreed on 58 decisions (87.9% observed agreement), yielding a Cohen's κ value of 0.642, indicating substantial agreement.[11] All eight disagreements were resolved through consensus.

Eligibility

A comprehensive evaluation of full-text articles was conducted to confirm their relevance to the study. Articles were excluded based on criteria such as irrelevance to the research topic, unclear methodologies, or deviations from the scope of the study. This process was followed by a detailed data appraisal to establish the eligibility of the remaining articles (Figure 1).

Risk of Bias and Quality Assessment

The articles were evaluated by two independent experts (NAT and MAK), focusing on the study design, methodology, sample size representativeness, and data analysis. The methodological quality of the observational studies was independently assessed by two reviewers (NEHAR and WNFWMZ) using the Newcastle–Ottawa Scale (NOS), which evaluates three domains: Selection, Comparability, and Exposure, with a maximum score of nine stars. Any scoring discrepancies were resolved through consensus with a third reviewer. Overall, the studies ranged from fair to good quality based on the NOS. Most studies demonstrated appropriate selection of cases and controls, although several lacked clear adjustments for confounding factors. The final NOS ratings are presented in Table II. Disagreements in extracted data were resolved through discussion, with a third reviewer arbitrating if necessary. Inter-rater reliability was also evaluated for the data elements. The non-human mechanistic studies (e.g., mouse and Drosophila models) were not assessed using NOS, as this tool is designed explicitly for human observational studies. These studies were instead narratively evaluated.

RESULTS

Background of Selected Studies

The study examined a total of 41 research articles which evaluated fifteen apolipoprotein-related genes. The frequency analysis revealed that the majority of the articles focused on *APOE* (n=25), making it the most heavily studied. This was followed by apolipoprotein L, *APOL* (n=6), apolipoprotein A, *APOA* (n=4), and apolipoprotein D, *APOD* (n=4). In contrast, other apolipoprotein genes, such as apolipoprotein C, *APOC* (n=2), apolipoprotein E receptor 2, *APOER2* (n=2), and apolipoprotein B editing enzyme catalytic, *APOBEC* (n=1), were investigated less frequently. Some studies investigated multiple genes reflecting varying research interests.

Thematic analysis was performed to provide a clearer

Table I: Search strings used in the selected database

Databases	Keywords used
Scopus	(TITLE-ABS-KEY ("genetic" OR "genetical" OR "genetically" OR "genetics" OR "genetics" OR "genetics") AND TITLE-ABS-KEY ("schizophre-nia" OR "schizophrenia" OR "schizophreni-as" OR "schizophrenia s") AND TITLE-ABS-KEY ("apolipopro-teine" OR "apolipoproteins" OR "apolipopro-teins" OR "apolipoprotein")) AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))
PubMed	("genetic"[All Fields] OR "genetical"[All Fields] OR "genetically"[All Fields] OR "genetics"[MeSH Subheading] OR "genetics"[All Fields] OR "genetics"[MeSH Terms] OR ("genetic"[All Fields] OR "genetical"[All Fields] OR "genetically"[All Fields] OR "genetics"[MeSH Subheading] OR "genetics"[All Fields] OR "genetics"[MeSH Terms])) AND ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields]) AND ("apolipoproteine"[All Fields] OR "apolipoproteins"[MeSH Terms] OR "apolipoproteins"[All Fields] OR "apolipoprotein"[All Fields])

Table II: Quality Assessment of All Included Studies Using Newcastle-Ottawa Scale

No	Study	Selection (0-4)	Comparability (0-2)	Exposure (0-3)	Total (0-9)	Quality
1	Moberg et al. (2006)[13]	4	2	2	8	High
2	Kampman et al. (2004)[14]	4	1	2	7	High
3	Kecmanovic et al. (2010)[15]	4	1	2	7	High
4	Martorell et al. (2008)[16]	3	1	2	6	Moderate
5	Akanji et al. (2009)[17]	3	1	2	6	Moderate
6	Tovilla-Zarate et al. (2009)[18]	2	1	2	5	Moderate
7	Al-Asmary et al. (2015)[19]	3	1	2	6	Moderate
8	Vila-Rodriguez et al. (2011)[20]	0	0	2	2	Low*
9	Knickmeyer et al. (2014)[21]	0	0	2	2	Low*
10	Ormel et al. (2020)[22]	0	0	2	2	Low*
11	Zhang et al. (2006)[23]	4	1	2	7	High
12	Takahashi et al. (2008)[24]	4	1	2	7	High
13	Carrera et al. (2010)[25]	4	1	2	7	High
14	McGhee et al. (2005)[26]	3	1	2	6	Moderate
15	Dong et al. (2012)[27]	3	1	2	6	Moderate
16	Lee et al. (2013)[28]	3	1	2	6	Moderate
17	Hwang et al. (2013)[29]	3	1	2	6	Moderate
18	Shishido et al. (2023)[30]	3	1	2	6	Moderate
19	Suzuki et al. (2008)[31]	0	0	2	2	Low*
20	Tomita et al. (2007)[32]	0	0	2	2	Low*
21	Smith et al. (2008)[33]	3	2	2	7	High
22	Hong et al. (2012)[34]	3	2	2	7	High
23	Ban et al. (2017)[35]	3	2	2	7	High
24	Clark et al. (2009)[36]	3	1	2	6	Moderate
25	Vik-Mo et al. (2009)[37]	3	1	2	6	Moderate
26	Kao et al. (2014)[38]	2	2	2	6	Moderate
27	Li et al. (2020)[39]	2	2	2	6	Moderate
28	Fan et al. (2021)[40]	3	1	2	6	Moderate
29	Li et al. (2021)[41]	2	2	2	6	Moderate
30	Li et al. (2021)[42]	2	2	2	6	Moderate
31	Verbrugghe et al. (2012)[43]	4	2	2	8	High
32	Vila-Rodriguez et al. (2017)[44]	4	2	2	8	High
33	Hansen et al. (2006)[45]	3	2	2	7	High
34	Ward et al. (2017)[46]	3	2	2	7	High
35	Walker et al. (2006)[47]	3	1	2	6	Moderate
36	Boer et al. (2010)[48]	3	1	2	6	Moderate
37	Kurian et al. (2011)[49]	3	1	2	6	Moderate
38	Jonas et al. (2019)[50]	2	2	2	6	Moderate
39	Rao et al. (2021)[51]	3	1	2	6	Moderate
40	Liebers et al. (2016)[52]	2	2	2	6	Moderate
41	Rapp et al. (2010)[53]	0	0	2	2	Low*

Note: Quality categories: High (7-9), Moderate (5-6), Low (0-4).
* Different study design (not traditional case-control)

understanding of the main points of the articles.[54] The four main themes synthesised from the selected studies include: (1) Apolipoprotein E variants and schizophrenia susceptibility, (2) Apolipoprotein-related genetic interaction in schizophrenia, (3) Apolipoprotein variations' influence on lipid metabolism in schizophrenia, and (4) Apolipoprotein variants and cognitive function in schizophrenia. The results of each theme are discussed in the following sections.

Table III: Classification of articles according to Theme 1

Author (Year)	Author (Year)	Sample Size (n)	Methods	Genetic analysis	Genes	Key findings	p-value
Ormel et al.[22] (2020)	In vitro study (induced microglia-like cells)	20 Scz 20 Ctrl	RNAseq	GE	*APOE*	No association observed in iMG model derived from schizophrenia patients.	$p > 0.05$
Al-Asmary et al.[19] (2015)	Case-control	180 Scz 200 Ctrl	PCR	SNP genotyping	*APOE* (ε2, ε3, ε4)	*APOE*-ε2 allele increase, while the ε3 allele decrease in schizophrenia patients.	$p \leq 0.01$
Knickmeyer et al.[21] (2014)	Cross-sectional (neonate's brain imaging)	248 neonates with parental psychiatric history	MALDI-TOF MS	SNP. genotyping	*APOE* (ε2, ε3, ε4)	*APOE* ε3ε4 heterozygotes show reductions in brain volumes.	$p < 0.01$
Vila-Rodriguez et al.[20] (2011)	Case-control (postmortem brain study)	35 Scz 35 Ctrl	PCR-RFLP	SNP genotyping	*APOE* (ε2, ε3, ε4)	Similar allele and genotype frequencies as general population.	$p > 0.05$
Kecmanović et al.[15] (2010)	Case-control	76 Scz 82 Ctrl	PCR-RFLP	SNP genotyping	*APOE* (ε2, ε3, ε4)	No association in allele and genotype frequencies in schizophrenia.	$p > 0.05$
Akanji et al.[17] (2009)	Case-control	207 Scz 165 Ctrl	PCR-RFLP	SNP genotyping	*APOE* (ε2, ε3, ε4)	*APOE* ε3ε2 genotype and allele ε2 are less frequent in patients compared to controls.	$p = 0.04$
Tovilla-Zarate et al.[18] (2009)	Family-based association study	60 families (sibling pairs)	PCR-RFLP	SNP genotyping	*APOE* (ε2, ε3, ε4)	*APOE*-ε3 allele is associated with schizophrenia patients, especially in females, whereas haplotypes of *APOE* ε3/*APOE*-219 G/T are associated with reduced schizophrenia risk in males. The *APOE*-ε2 allele is protective against early-onset schizophrenia.	$p < 0.05$
Martorell et al.[16] (2008)	Case-control (SNP association study)	585 Scz 615 Ctrl	MALDI-TOF MS	SNP genotyping	*APOE* (ε2, ε3, ε4)	There is no association found between the APOE polymorphism and schizophrenia.	$p > 0.05$
Moberg et al.[13] (2006)	Case-control (olfactory function study)	28 Scz 26 Ctrl	PCR	SNP genotyping	*APOE* (ε2, ε3, ε4)	There is no association between *APOE* and odour identification in the patients.	$p > 0.05$
Kampman et al.[14] (2004)	Case-control	94 Scz 98 Ctrl	RT-PCR	SNP Genotyping	*APOE* (ε2, ε3, ε4)	*APOE* ε3 linked to later age of onset and the *APOE* ε4/ε4 to early onset in schizophrenia.	$p < 0.05$

*Note: Scz = Schizophrenia, Ctrl = Control, GE = Gene expression, SNP = Single nucleotide polymorphism, PCR = Polymerase chain reaction, RT = Real time, RFLP = Restriction Fragment Length Polymorphism, MALDI-TOF MS = Matrix Assisted Laser Desorption and Ionisation Time of Flight Mass Spectrometry

Theme 1: Apolipoprotein E *(APOE)* in Schizophrenia Susceptibility

Ten studies highlight the significance of *APOE* polymorphism and gene expression in the progression of schizophrenia, as detailed in Table III. In an in vitro model study, Ormel et al.,[22] reported no significant differences in *APOE* gene expression in induced microglia-like cells derived from schizophrenia patients. Several other studies focused on *APOE* polymorphisms, particularly the *APOE* ε4 allele associated with schizophrenia vulnerability.[14] Al-Asmary et al.[19] and Tovilla-Zarate et al.,[18] did not find a significant connection between the *APOE* ε4 allele and schizophrenia. Al-Asmary et al.[19] found *APOE* ε2 allele was associated with an increased risk of schizophrenia, whereas the *APOE* ε3 allele was associated with a decreased risk. Meanwhile, Tovilla-Zarate et al.[18] reported that the *APOE* ε3 allele was associated with an increased risk, while the *APOE* ε2 allele was protective against early-onset schizophrenia. A few studies yielded no association between *APOE* alleles and schizophrenia.[13,16,20] Additionally, Kampman et al.,[14] suggested the *APOE* ε3 allele as a protective factor and the *APOE* ε4 allele as a risk factor for schizophrenia. Kecmanović et al.,[15] explored the potential therapeutic response of the *APOE* ε4 allele to typical antipsychotics.

Across the ten studies investigating *APOE* variants, five reported statistically significant results ($p<0.05$), while five found no significant effects (Figure 2). Among the primary studies, three identified increased schizophrenia-related risk susceptibility, including *APOE* ε4-associated structural brain alterations. Two studies reported protective effects linked with the ε2 or ε3 alleles. The remaining studies showed no significant differences in allele or genotype distributions among the schizophrenia and control groups.

Table IV: Classification of articles according to Theme 2

Author (Year)	Study Design	Sample Size (n)	Method	Type of Genetic Analysis	Genes	Key findings	p-value
Shishido et al.[30] (2023)	Case–control (Postmortem brain study)	25 Scz 21 Ctrl	RNA Seq	GE	*APOA (APOA1* and *APOA2)*	*APOA1* is highly expressed in high-stress response schizophrenia	NA
Hwang et al.[29] (2013)	Case-control (Postmortem brain study)	33 Scz 34 Ctrl	RT-PCR	GE	*APOL (APOL1)*	*APOL1* is upregulated in schizophrenia.	p = 0.02
Lee et al.[28] (2013)	GWAS pathway analysis	1378 Scz 1351 Ctrl	ICSN pathway analysis	Functional SNP annotation	*APOL (APOL2)*	*APOL2* was found in schizophrenia.	p < 0.01
Dong et al.[27] (2012)	Case-control (Postmortem brain study)	6 Scz + 6 bip 12 Ctrl	RT-PCR	GE	*APOBEC (APOBEC3A* and *APOBEC3C)*	*APOBEC3A* and *APOBEC3C* are downregulated in the parietal cortex in schizophrenia patients.	p < 0.01
Carrera et al.[25] (2010)	Case-control	301 Scz 604 Ctrl	MALDI-TOF MS	SNP genotyping	*APOL (APOL1)*	No association found between *APOL1* variants and schizophrenia.	p > 0.05
Suzuki et al.[31] (2008)	Case-control	40 Scz (20 Medicated and 20 drug naïve) 40 Ctrl	RT-PCR	GE	*APOER2*	*APOER2* mRNA levels decreased after six months of antipsychotic treatment.	p < 0.01
Takahashi et al.[24] (2008)	Family-based association	377 families	MALDI-TOF MS	SNP genotyping	*APOL (APOL1-6)*	*APOL1,2* and *4* SNPs are significantly involved with schizophrenia.	p < 0.01
Tomita et al.[32] (2007)	Case-control	845 Scz 707 Ctrl	PCR-RFLP	SNP genotyping	*APOL (APOL1-6)*	No significant observations in individual SNPs. The combination of GG genotypes of SNP VI-1 and SNP V-2 is protective against schizophrenia.	p < 0.01
Zhang et al.[23] (2006)	Case-control	424 Scz 473 Ctrl	PCR	SNP genotyping	*APOD*	No association was found between the polymorphism of *APOD* and schizophrenia.	p > 0.05
McGhee et al.[26] (2005)	Case-control (Postmortem brain study)	219 Scz 230 Ctrl	SNaPshot	SNP genotyping	*APOL (APOL1,2* and *4)*	No association was found between the polymorphism of *APOL* family genes and schizophrenia.	p > 0.05

*Note: Scz=Schizophrenia, Ctrl= Control, GE=Gene expression, SNP = Single nucleotide polymorphism, PCR = Polymerase chain reaction, RT = Real-time, RFLP = Restriction Fragment Length Polymorphism, RNA Seq = RNA Sequencing, ICSN = Integrated Candidate SNP Network, MALDI-TOF MS = Matrix Assisted Laser Desorption and Ionisation Time of Flight Mass Spectrometry, SNAPshot = Single Nucleotide Primer Extension

Theme 2: Apolipoprotein-related Genetic and Molecular Interactions in Schizophrenia

Ten studies assessed the primary role of apolipoprotein-related genes in contributing to the pathophysiology of the disorder, as summarised in Table IV. Takahashi et al.,[24] reported significant associations between *APOL* family genes (*APOL1, APOL2*, and *APOL4*) and schizophrenia. Similarly, Hwang et al.,[29] identified *APOL1* as significantly involved in the disorder, while Lee et al.,[28] highlighted the role of *APOL2*. Despite these associations, Carrera et al.[25] and McGhee et al.[26] found no significant association between *APOL* family gene polymorphisms and schizophrenia. Through binomial and random permutation (BRP) statistical analysis on seven SNPs in the *APOL* gene cluster, Tomita et al.,[32] found consistent protective allele or genotype interactions across two independent datasets, although no significant risk factors were identified based on their analysis.

The *APOA1* was upregulated in high-stress response schizophrenia.[30] Additionally, Suzuki et al.,[31] noted a downregulation of *APOER2* mRNA after six months of antipsychotic treatment. Additionally, Dong et al.,[27] found a significant decrease in *APOBEC3A* and *APOBEC3C* gene expression in the parietal cortex of individuals with schizophrenia, suggesting potential alterations in DNA demethylation mechanisms that increase the schizophrenia risk. Zhang et al.,[23] investigated the relationship between *APOD* single-nucleotide polymorphisms (SNPs) and schizophrenia but found no association.

Across the ten studies assessing apolipoprotein-related gene family variants, four reported significant associations with schizophrenia risk, while the remaining studies showed either no association or only trends (Figure 3). Major findings were primarily concentrated in *APOL1, APOL2, APOL4, APOBEC,* and *APOER2,* reporting risk-increasing effects. One study on *APOA* expression demonstrated protective effects on schizophrenia.

Table V: Classification of articles according to Theme 3

Author	Study Design	Sample Size (n)	Method	Type of genetic analysis	Genes	Key findings	p-value
Fan et al.[40] (2021)	Cross-sectional pharmacogenetic	1979 Scz	RT-PCR	SNP genotyping	*APOA (APOA1)*	*APOA1* (rs5072) associated with increased triglyceride (TG) levels in schizophrenia patients treated with combination of antipsychotic drugs.	p = 0.03
Li et al.[42] (2021)	Case-control	301 Scz 156 Ctrl	ARMS-PCR	SNP genotyping	*APOE* (ε4)	*APOE* ε4 associated with hyperlipidaemia and diabetes.	p < 0.05
Li[41] (2021)	Cross-sectional	301 Scz	ARMS-PCR	SNP genotyping	*APOE* (ε2)	*APOE* ε2 genotype associated with lower LDL (low-density lipoprotein) levels.	p < 0.01
Li et al.[39] (2020)	Cross-sectional	301 Scz	ARMS-PCR	SNP genotyping	*APOE* (ε3)	*APOE* ε3 variant associated with higher LDL and hyperlipidaemia.	p = 0.03
Ban et al.[35] (2017)	Cross-sectional	300 Scz	PCR-LDR	SNP genotyping	*APOE* (ε2, ε3, ε4)	*APOE*-ε2 allele associated with lower LDL level and cholesterol.	p < 0.01
Kao et al.[38] (2014)	Prospective 3-month trial	129 Scz	PCR	SNP genotyping	*APOE* (ε4)	*APOE* ε4 is positively correlated with increased TC levels under paliperidone	p < 0.01
Hong et al.[34] (2012)	Cross-sectional pharmacogenetic	466 Scz	MALDI-TOF MS	SNP genotyping	*APOA* (APOA5)	Two alleles of *APOA5* (–1131C and –3G) associated with the increased of TG in the patients treated with risperidone.	p < 0.01
Clark et al.[36] (2009)	Case-control	427 Scz	PCR-RFLP	SNP genotyping	*APOE*	*APOE* variants influenced diabetes under medications.	p = 0.04
Vik-Mo et al.[37] (2009)	In vitro cell culture	4 in vitro cell culture	RT-PCR z	GE	*APOE*	The expression of *APOE* increased in cell culture on treatment with clozapine, olanzapine, haloperidol and imipramine.	p < 0.01
Smith et al.[33] (2008)	Cross-sectional pharmacogenetic	189 Scz	PCR	SNP genotyping	*APOC (APOC3)* and *APOA (APOA5)*	The rare alleles and haplotypes of *APOA5* and *APOC3* genes associated with varied cholesterol and triglyceride levels in patients treated with specific antipsychotics.	p < 0.05

*Note: Scz=Schizophrenia, Ctrl= Control, GE=Gene expression, SNP = Single nucleotide polymorphism, PCR = Polymerase chain reaction, RT = Real-time, RFLP = Restriction Fragment Length Polymorphism, ARMS = Amplification refractory mutation system, LDR= ligase detection reaction, MALDI-TOF MS = Matrix Assisted Laser Desorption and Ionisation Time of Flight Mass Spectrometry

Theme 3: Apolipoprotein Variations Influence on Lipid Metabolism in Schizophrenia

Table V shows the relationship between apolipoprotein genes and lipid metabolism in individuals with schizophrenia, focusing on lipid profiles, the impact of antipsychotic medications, and the clinical outcomes. The *APOE* ε4 allele was significantly associated with hyperlipidaemia in elderly schizophrenia patients. At the same time, the *APOE* ε3 homozygous genotype was associated with higher concentrations of low-density lipoprotein (LDL) and hyperlipidaemia compared to the heterozygous *APOE* ε3 genotype.[39,42] The *APOE* ε2 allele was discovered to be a protective factor, associated with lower LDL and cholesterol levels in elderly schizophrenia patients.[35,41]

Regarding antipsychotic treatments, a significant upregulation of *APOE* expression was reported.[37] Specifically, Kao et al.,[38] discovered that the *APOE* ε4 is positively correlated with increased TC levels under paliperidone. Similarly, the association between *APOE* variants and cardiovascular risk is pronounced in patients on antipsychotic medication.[36] Additionally, *APOA1* polymorphism has been associated with elevated triglyceride (TG) levels in patients treated with a combination of second-generation antipsychotic drugs (SGAs).[40] Specific variants of *APOA5* (-1131C and -3G) are linked to increased TG in patients on risperidone,[34] while another variant is associated with increased total cholesterol (TC).[33] The specific *APOA5* variant (-1131T/C) affects TC levels depending on the antipsychotic used.[33] Moreover, *APOC3* variants displayed differential impacts of TG levels, whereby the gene variants were associated with reduced TG levels in patients on olanzapine or clozapine. In contrast, other variants are associated with increased TG levels in patients on first-generation antipsychotics (FGAs).[33]

From among the ten studies investigating apolipoprotein gene variants and metabolic effects, one study was excluded,[37] as it did not relate the genetic variants to the lipid profile. One of the studies reported no significant findings, while the remaining eight studies reported statistically significant metabolic associations (Figure 4). Significant findings most commonly involved triglyceride outcomes, where *APOA5, APOC3, APOE* and *APOA1* variants demonstrated metabolically relevant changes. In contrast, several studies reported no triglyceride or cholesterol effects for *APOE* ε2 or ε3 alleles. LDL findings were mixed, with both increases and decreases observed depending on the research and analysis. Protective patterns were observed for the *APOE* ε2 allele.

Table VI: Classification of articles according to Theme 4

Author	Study Design	Sample Size (n)	Method	Genetic Analysis	Genes	Key findings	p-value / CFG score
Rao et al.[51] (2021)	Case-control	637 Scz 467 Ctrl	MALDI-TOF-MS	SNP genotyping	Gene: *APOE* Proteins: *APOA* (APOA1) and APOB	APOA1 and APOB are significantly upregulated with positive cognitive performance and are influenced by the *APOE* (rs429358) polymorphism.	p < 0.01
Jonas et al.[50] (2019)	Longitudinal study	116 Scz	Microarray	SNP genotyping	*APOE* (ε4)	*APOE*-ε4 allele associated with increased escalating psychotic symptoms in late adulthood.	p < 0.01
Vila-Rodriguez et al.[44] (2017)	Case-control	86 Scz 39 Ctrl	RT-PCR	SNP genotyping	*APOE* (ε4)	*APOE*- ε4 allele associated with improved verbal memory.	p < 0.01
Ward et al.[46] (2017)	Cross-sectional pharmacogenetic	122 Scz	RT-PCR	SNP Genotyping	*APOE* (ε2, ε3, ε4)	*APOE*- ε4 allele is linked with poor verbal memory.	p < 0.01
Liebers et al.[52] (2016)	Longitudinal study	8616 Scz	Microarray	SNP genotyping	*APOE* (ε4)	*APOE*- ε4 allele associated with cognitive decline.	p < 0.01
Verbrugghe et al.[43] (2012)	Case-control	336 Scz 172 Ctrl	Microarray and RT-PCR	SNP genotyping and GE	*APOE* and *APOER2*	The downregulation of *APOER2* is linked with cognitive impairment.	p = 0.03
Kurian et al.[49] (2011)	Longitudinal study	31 Scz	Microarray	GE	*APOE*	*APOE* is decreased in high delusion states among schizophrenia.	CFG score 5.5 for delusions biomarker
Boer et al.[48] (2010)	Experimental animal model	10 APOD–/– mice 10 Wildtype (WT) mice	-	None	*APOD*	*APOD* deficiency is associated with decreased density of kainate and AMPA receptors.	p < 0.01
Rapp et al.[53] (2010)	Cross-sectional (Brain postmortem study)	110 Scz	PCR	SNP genotyping	*APOE* (ε4)	*APOE* - ε4 variant associated with dementia severity among schizophrenia patients.	p < 0.01
Hansen et al.[45] (2006)	Case-control	343 Scz 346 Ctrl	RT-PCR	SNP genotyping	*APOD*	*APOD* is associated with poor long-term clinical outcomes.	p = 0.04
Walker et al.[47] (2006)	Experimental animal study	≥100 transgenic flies ≥100 control flies	RT-PCR	GE	*APOD* homologs	*APOD* homologs have a protective effect against behavioural deficits.	p < 0.01

*Note: Scz=Schizophrenia, Ctrl= Control, GE=Gene expression, SNP = Single nucleotide polymorphism, PCR = Polymerase chain reaction, RT = Real-time, MALDI-TOF MS = Matrix Assisted Laser Desorption and Ionisation Time of Flight Mass Spectrometry

Theme 4: Apolipoprotein Variants and Cognitive Functions in Schizophrenia

This theme highlights the role of apolipoprotein genes on cognitive function among patients with schizophrenia (Table VI). Several studies have discovered that *APOE* ε4 is associated with cognitive impairments in adult schizophrenia.[46,50,52,53,55] Furthermore, gene expression studies have shown that *APOE* expression was downregulated in schizophrenia patients during delusional states.[49] Contrary to earlier findings, Vila-Rodriguez et al.,[44] reported that the *APOE* ε4 allele improves cognitive outcomes. Additionally, Rao et al.,[51] emphasised the significant role of *APOE* in the upregulation of APOA1 and APOB proteins, which could potentially contribute to improved cognitive performance.

Research on the *APOD* gene in schizophrenia has yielded contrasting findings. Boer et al.[48] and Walker et al.,[47] identified *APOD* as a potential protective factor against the development of schizophrenia. In contrast, Hansen et al.,[45] found no significant difference between *APOD* expression and schizophrenia, although *APOD* was related to poor long-term cognitive outcomes due to antipsychotic drugs. Additionally, *APOER2* was found to be significantly downregulated in individuals with schizophrenia who exhibit cognitive deficits, indicating the important role of the gene in the modulation of mental functions in this population.[43]

Eleven studies investigating apolipoprotein gene variants and cognitive outcomes, with ten reporting statistically

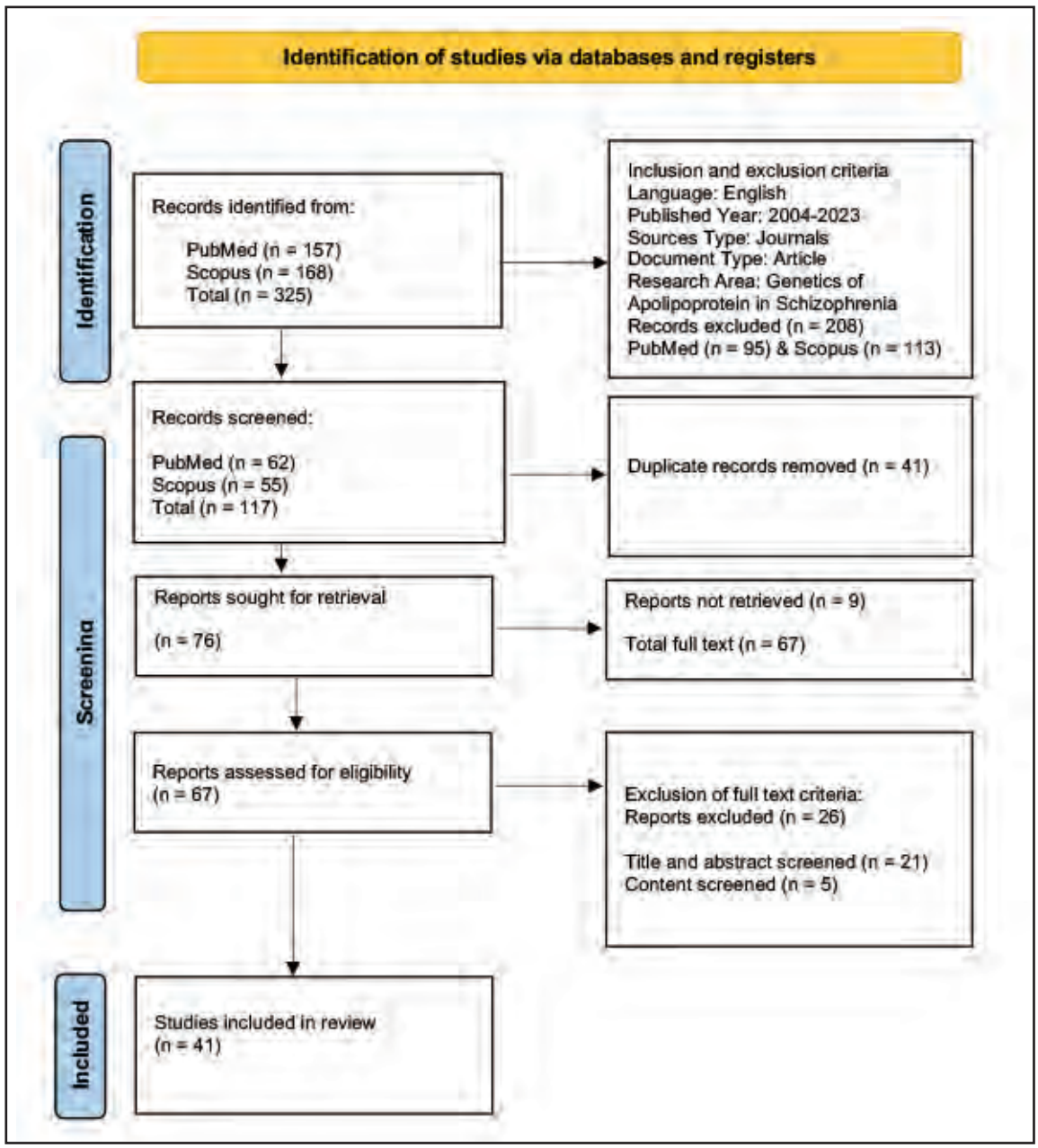

Fig. 1: PRISMA flowchart representing the outline search strategy and outcome of systematic literature review.[12]

significant associations ($p<0.05$) and one showing a trend toward impairment with increased *APOE* expression (Figure 5). The most important findings involved *APOE* ε4, which was associated with poorer cognitive performance across domains such as verbal memory, attention, and dementia severity in multiple studies. *APOER2* downregulation was also implicated in cognitive impairment, while *APOD* variants demonstrated both protective and adverse cognitive associations depending on the study context.

DISCUSSION

Theme 1: Apolipoprotein E *(APOE)* in Schizophrenia Susceptibility

APOE polymorphisms in schizophrenia reveal a complex relationship between different alleles (ε2, ε3, and ε4) and susceptibility to schizophrenia, influenced by their roles in lipid metabolism and neuroinflammation. The ε4 allele is identified as a potential risk associated with modulating brain structure[21] and early-onset schizophrenia,[14] while the ε2 allele is identified as a potential protective factor in schizophrenia.[17,18] These alleles demonstrated various effects due to their efficiency in lipid homeostasis,[56] with the ε2 allele exhibiting the highest efficiency, followed by the ε3 and ε4 allele.[56] Dysregulation in lipid homeostasis leads to lipidation and contributes to neuroinflammation, known to be a factor in the pathophysiology of schizophrenia.[56,57] However, contradictory findings showed that the ε2 and ε3 alleles also contribute to the risk factors of schizophrenia in different populations,[18,19] highlighting the importance of considering genetic and ethnic diversity in the development of schizophrenia. Additionally, several studies could not find an

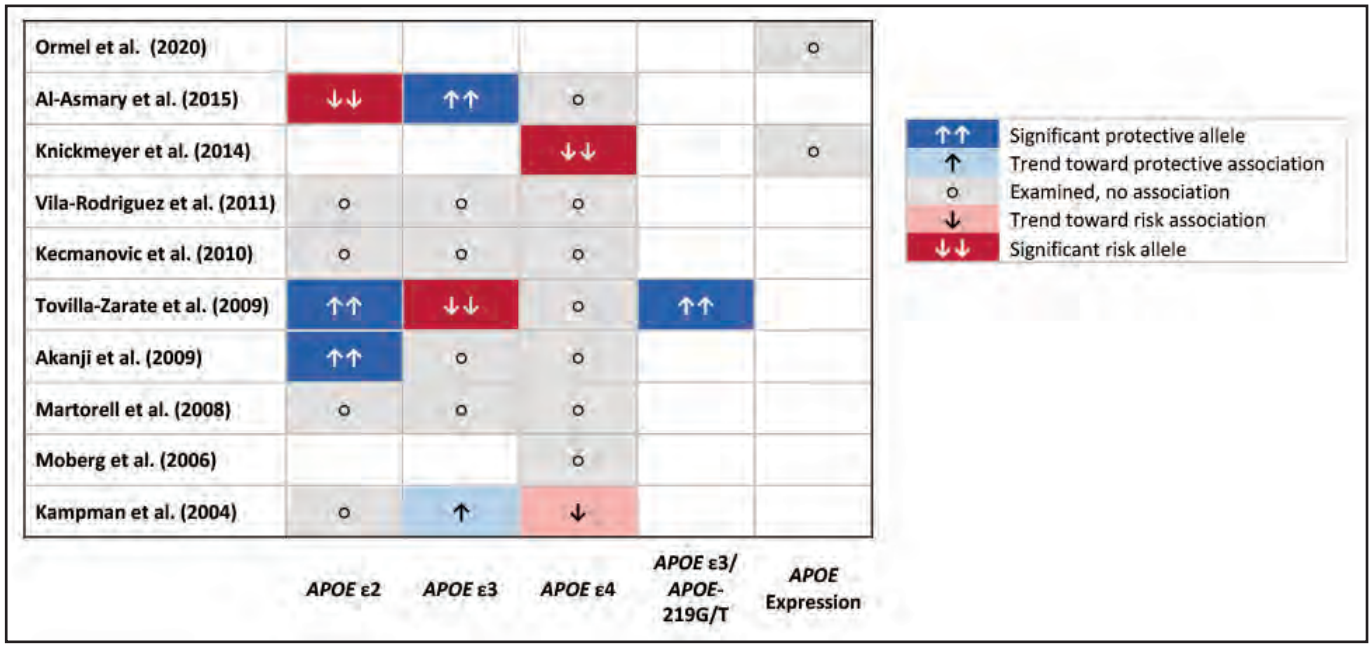

Fig. 2: Heatmap of 10 studies in Theme 1. Risk allele refers to an allele associated with increased schizophrenia susceptibility (higher frequency in cases). Protective allele refers to an allele associated with reduced susceptibility (lower frequency in cases)

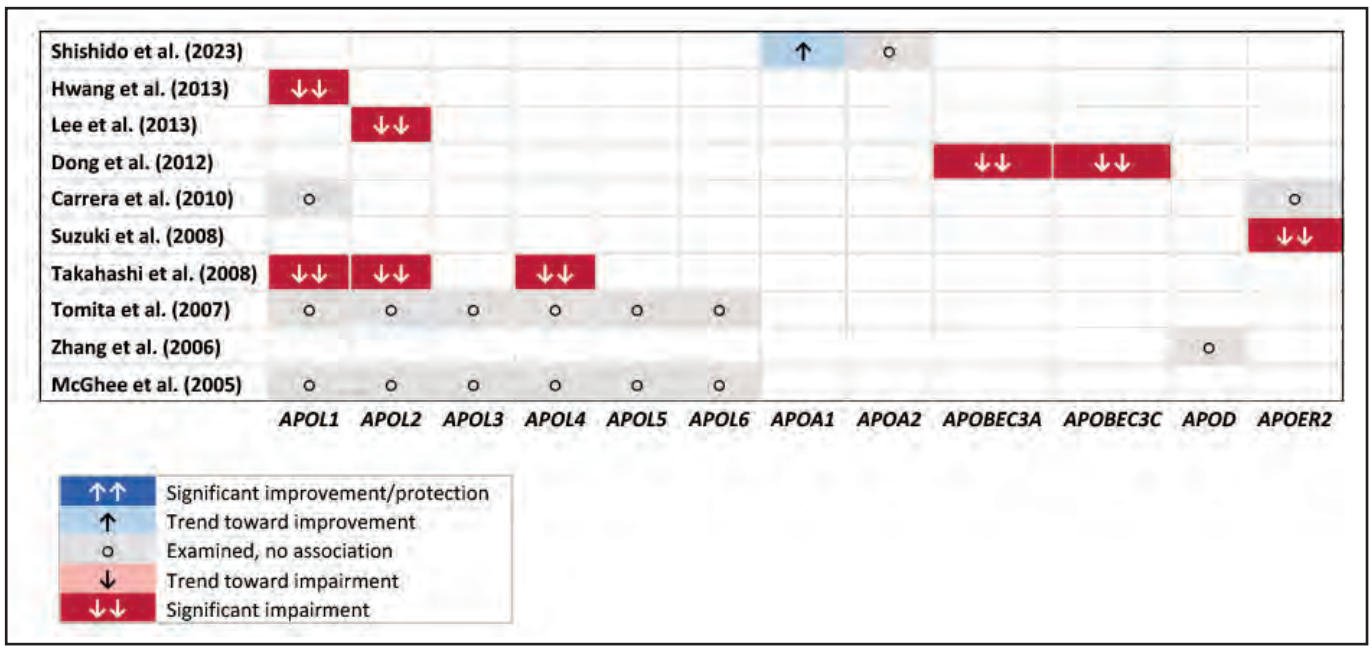

Fig. 3: Heatmap of 10 Studies in Theme 2 showing apolipoprotein-related variants in schizophrenia risk

association between *APOE* variants and the susceptibility to schizophrenia,[16,20] suggesting that *APOE* genes exert a small effect, which requires a large sample size to be significantly detected.[7]

Understanding the cellular and molecular phenotypes in schizophrenia may help generate hypotheses on the potential role of *APOE* expression and neuroinflammation in the disorder's pathogenesis. Microglia play a critical role in neuroinflammation and neurodevelopment, which are important in this context.[58] While *APOE* gene expression in induced microglia-like cells (iMG) showed no difference between schizophrenia patients and controls, mass cytometry revealed a significant upregulation of APOE protein levels in schizophrenia patients.[22] Additionally, iMG derived from schizophrenia showed an increased response to lipopolysaccharide (LPS) stimulation, which leads to the high secretion of pro-inflammatory cytokines TNF-α,[22] highlighting the association of APOE with inflammation. The neuroinflammatory state, driven by activated microglia, contributes to structural brain changes, such as reduced hippocampal volume, in schizophrenia.[59] These observations

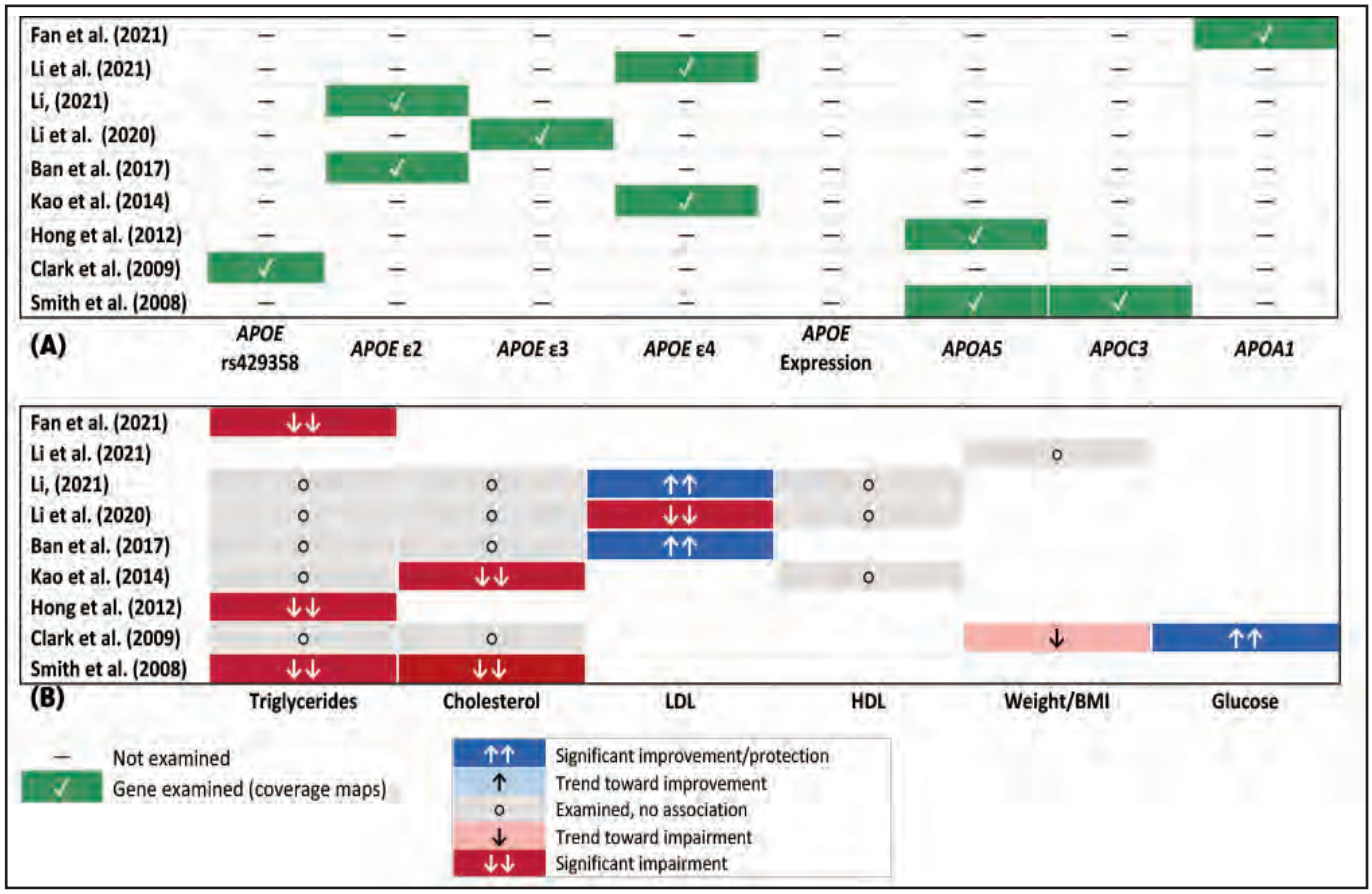

Fig. 4: Heatmap of 9 studies in Theme 3 showing (A) gene coverage and (B) metabolic effects associated with apolipoprotein related variants

suggest a possible link between APOE protein levels, neuroinflammation and schizophrenia-related phenotypes that may contribute to the disorder's pathogenesis.

Antipsychotic medications are commonly used to treat schizophrenia patients, although therapeutic responses vary among individuals.[60] One study suggested an association between the *APOE* ε4 allele and the influence of the first-generation antipsychotics in schizophrenia patients positively,[15] indicating better treatment outcomes for the carriers of this allele. However, different generations of antipsychotic drugs may vary in the mechanism of action, resulting in various adverse effects in patients.[61] This finding highlights the importance of considering the possibility that genetic variations in antipsychotic drug response, reinforcing the value of personalised medicine approaches in psychiatric care.[62]

Apolipoprotein E receptor type 2 (APOER2) is the target for reelin, which is essential for neuronal development and synaptic plasticity.[63] The binding of APOER2 to the reelin facilitates the connection between neurons in brain development.[64] The reduction of *APOER2* may affect neuroinflammatory signalling, leading to less neuronal damage.[65,66] Even though there was no association between *APOER2* mRNA and drug naïve patients, the mRNA level was downregulated after six months of antipsychotic treatments,[31] suggesting the treatment could modulate the expression of *APOER2* and further reduce the neuronal damage. Therefore, *APOER2* may be a potential drug target to address neuroinflammation and schizophrenia severity. However, the long-term effect of medications on the reelin signalling pathway, impairing the synaptic plasticity, requires further investigation.

Theme 2: Apolipoprotein-related genetic and molecular interactions in schizophrenia

Other apolipoprotein-related genes that have been identified to be associated with schizophrenia include *APOL, APOD,* and *APOA*. The *APOL* gene family consists of six genes that have been studied for their potential involvement in schizophrenia, which identified the associations of *APOL1, APOL2,* and *APOL4* with schizophrenia,[24,28,29] which aligns with their previously described pro-apoptotic properties.[67–71] The studies reported that dysregulation of apoptosis could contribute to excessive cell loss and lead to neuroinflammation.[57,72] However, considering the contrasting results reported by Carrera et al.,[25] and McGhee et al.,[26] who found no association between *APOL* family and schizophrenia, highlights the complexity of *APOL* genes. Additionally, the protective effect and the genotype interactions may reduce the severity of the disorder.[32] These findings demonstrate that the involvement of *APOL* genes in schizophrenia remains inconsistent.

APOD is known to participate as a neuroprotector in lipid metabolism and myelin maintenance, which is crucial for brain development.[73] However, the genetic study that explored *APOD* SNPs and schizophrenia failed to find the association in Han Chinese populations, which may be due to factors such as small sample size and methodological approaches.[23] The authors suggested that one methodological approach to address this issue includes the use of family-based association studies to reduce biases by eliminating potential confounding factors.[74] Moreover, an appropriate sample size is crucial in genetic studies, as a small sample size may fail to identify a true association.[75] *APOD* was suggested to have a possible neuroprotective factor, but its genetic association with schizophrenia remains unclear.

Chronic stress influences the progression of schizophrenia,[76] by forming oxidative stress (OS) and reactive oxygen stress (ROS), which activates the release of pro-inflammatory cytokines that exacerbate neuronal damage.[77] *APOA1* is a high-density lipoprotein that plays roles in antioxidant and anti-inflammatory functions.[78] The elevated gene expression of *APOA1* in high-stress response schizophrenia,[30] highlights their interactions with the environment, influencing the pathophysiology of the disorder. Hence, *APOA1* variable expression may have possible interactions with oxidative stress and inflammation pathways in schizophrenia and potentially act as protective factors against the disorder's susceptibility.

Epigenetic mechanisms such as DNA methylation play a vital role in influencing the progression of schizophrenia.[79,80] The downregulation of *APOBEC3A* and *APOBEC3C* in the brains of individuals with schizophrenia suggests potential epigenetic dysregulation.[27] The enzymes involved in DNA demethylation and the reduction may lead to incomplete demethylation,[81] resulting in gene silencing that interferes with the gene activities responsible for regulating brain function.[82–84] Thus, *APOBEC3A* and *APOBEC3C* are essential in regulating the epigenetic mechanism of DNA demethylation, ensuring normal brain function.

Theme 3: Apolipoprotein Variations Influence on Lipid Metabolism in Schizophrenia

Research on the association between *APOE* genes and clinical outcomes in schizophrenia has gained attention, particularly due to their implications for lipid metabolism. The three major alleles of *APOE*, ε2, ε3, and ε4, exert different effects on lipid metabolism.[85–87] The ε2 allele is the most efficient in transporting lipids, followed by ε3 and ε4.[88] The *APOE* ε2 allele has been found to be associated with lower LDL in elderly schizophrenia patients,[35,41] linking with reduced risks of hyperlipidaemia.[89] Its potential protective role may be due to its anti-inflammatory properties and its isoform-specific ability to promote clearance of plasma lipoprotein.[88] Conversely, the *APOE* ε4 increased the risk of hyperlipidaemia and diabetes in elderly schizophrenia patients,[42] suggesting the ε4 variant is susceptible to health complications such as hyperlipidaemia, diabetes mellitus, and cardiovascular disease.[90,91] The specific isoform has been associated with lower cholesterol efflux,[88] which may accumulate LDL in the blood circulation. While the ε2 allele has been suggested as a potentially protective allele and the ε4 allele as potentially a risk allele, the ε3 allele was the most common and is generally considered to be metabolically neutral in lipid metabolism.[56] However, Li et al.,[39] reported that the ε3 homozygotes were linked to higher LDL levels and an increased risk of hyperlipidaemia than the ε3 heterozygotes among individuals with schizophrenia.

Studies have found that *APOE* genetic and environmental factors may interact to modulate lipid metabolism in patients. The environmental factor that may influence *APOE* expression and its lipid metabolism includes antipsychotic drugs.[39] One previous study performed by Vik-Mo et al.,[37] found increased *APOE* expression in patients with schizophrenia treated with FGA (haloperidol), SGA (clozapine and olanzapine), and antidepressant (imipramine). Additionally, specific *APOE* variants were found to be associated with diabetes in patients on antipsychotics,[36]. This suggests that the observed correlation between *APOE* ε4 and elevated TC levels under paliperidone may reflect a gene-drug interaction rather than a simple genetic effect.[38] Thus, *APOE* genes may contribute to the lipid profile and clinical outcomes in schizophrenia, highlighting the importance of considering both genetic and environmental aspects, such as antipsychotic medications, in research.

Studies have demonstrated that apart from *APOE*, the genetic variations of *APOA1, APOA5,* and *APOC3* are also involved in this association. *APOA1* polymorphisms influenced TG levels in schizophrenia patients under combination drug therapy.[40] *APOA5* variants affect TG levels[34] and TC levels in schizophrenia patients treated with FGA and SGA.[33] Similarly, *APOA5* 1131 (T/C) and *APOC3* TG haplotypes were linked to increased TG levels in patients treated with FGA but decreased in those treated with olanzapine or clozapine.[33] In contrast, *APOC3* CC haplotypes have been discovered to be associated with increased TG in patients under olanzapine or clozapine.[33] These findings indicate the importance of genetic screening to identify high-risk individuals for antipsychotic-induced metabolic abnormalities, as apolipoprotein gene variations in regulating lipid metabolism are affected by the type of antipsychotic treatment.[92,93] Hence, personalised treatments in consideration of genetic profile may help to decrease the metabolic side effects in patients on medications.

Theme 4: Apolipoprotein Variants and Cognitive Function in Schizophrenia

Cognitive deficits, including memory deficits, attention issues, and problem-solving difficulties, influence the quality of schizophrenia patients.[94] *APOE* genes were found to be associated with modulating cognitive function in the disorder.[51] The *APOE* ε4 variant showed a decline in cognitive functions of schizophrenia patients,[46,50,52,53] which has been proposed to be due to the poor efficiency of lipid transportation,[95] leading to the disruption of synaptic plasticity, which is crucial for cognitive function.[96] This variant has been associated with increased amyloid-beta levels and plaque formation in the brain, further degraded inhibitory synapses, and cognitive decline.[97,98] In contrast, a study by Vila-Rodriguez et al.,[44] identified that the ε4 allele is involved in cognitive improvement in young schizophrenia patients, suggesting antagonistic pleiotropy. While the *APOE*

ε4 allele was found to be associated with improvement in cognitive abilities among young patients, it is associated with the increased risk of cognitive decline at a later age.[99] Hence, these findings suggest that *APOE* polymorphism may be associated with cognitive outcomes among individuals with schizophrenia.

APOD has been proposed to play a neuroprotective role in relation to cognitive functions in schizophrenia.[47,48] It has been reported to exhibit antioxidant activity, which may help reduce oxidative stress, apoptosis, and neuronal damage in neurodegenerative disorders.[100] While the *APOD* exerts its protective effects, it is involved in the cognitive declines in patients on treatment,[45] suggesting that antipsychotic drugs may dysregulate the *APOD* expression. The dysregulation of *APOD* may unintendedly impact cognitive functions, highlighting the complex interaction between *APOD* and cognitive function in schizophrenia.

The reelin signalling pathway, involving the interaction between reelin and APOER2, is critical in brain development,[101] highlighting the significance of its role in regulating cognitive function.[64,102] Hence, the dysregulation of this pathway, including the decreased expression of *APOER2,* has been reported to be associated with cognitive deficits.[43] The reduction of *APOER2* may influence the synaptic plasticity,[103,104] which could be relevant to the deterioration of cognitive functions.[105] Similarly, APOE interacts with APOER2 in the reelin signalling pathway to maintain synaptic plasticity by supporting membrane homeostasis and repairing injury in the brain.[104] The downregulation of *APOE* associated with high states of delusion in schizophrenia may have relevance for cognitive function.[49] These findings suggest that *APOE* and *APOER2* integrate to maintain the regulation of the reelin signalling pathway, as reduced expression of these genes may contribute to altered synaptic plasticity that has been linked to cognitive differences in schizophrenia.

LIMITATIONS

This review has several limitations. First, it uses only two databases (PubMed and Scopus). Relevant studies indexed in other sources, such as Embase, Web of Science, PsycINFO, and grey literature sources, may not have been included, potentially limiting the comprehensiveness of the evidence base. Variability across study designs, sample characteristics, and biological materials (e.g., blood, plasma, post-mortem brain tissue, and cells) limits direct comparability of results. Analytical methods also differed substantially from PCR-based genotyping to gene expression, introducing further methodological inconsistency. Although the review synthesises progress in genetic studies of apolipoproteins in schizophrenia, several research gaps remain. Most available studies focus mainly on *APOE*; other apolipoprotein genes, such as *APOA, APOD, APOL, APOC, APOER2,* and *APOBEC* families, remain understudied, limiting the understanding of their mechanistic roles and potential as treatment targets. Furthermore, the majority of the studies included are observational; therefore, the associations identified should not be interpreted as causal but rather as requiring validation in longitudinal or experimental investigations.

CONCLUSION

This review investigated the relationship between apolipoprotein genes and schizophrenia across four themes, discussing their roles in susceptibility, genetic interaction, lipid metabolism, and cognitive function. The researchers reported that apolipoprotein genes, particularly *APOE*, associate with the risk of schizophrenia. Additionally, apolipoproteins influence the lipid profile, resulting in metabolic disturbances in individuals with schizophrenia. Moreover, the connection between apolipoprotein genes and cognitive deficits was emphasised, which could assist to identify potential drug targets. Therefore, future research should aim to identify specific genetic biomarkers to enable improved therapeutic interventions in schizophrenia. However, limitations such as understudied genes and a lack of studies exploring biological mechanisms demonstrate the importance of future research to address these gaps. These associations suggest potential biomarker roles, although causality cannot be inferred from the current evidence base.

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